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09/403,075	05/10/2000	GARY L. JOHNSON	CPI-042CPUS	6811

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EXAMINER	
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ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/403,075	Applicant(s) Johnson
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 29, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-4, 12, 19, 20, 43, 50-54, 58-61, and 68-71* is/are pending in the application.

4a) Of the above, claim(s) *51* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4, 12, 19, 20, 43, 50, 52-54, 58-61, and 68-71* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Amendment filed November 29, 3002 (Paper No. 11) in response to the Office Action of May 22, 2002 (Paper No. 9) is acknowledged and has been entered. Previously pending claims 5-8, 16, 44-49, 55-57 and 62 have been canceled, claims 1-4, 12, 19, 43, 52-54, 58-59 have been amended and new claims (63-66), renumbered as per Rule 1.126 to 68-71 have been added. Claims 1-4, 12,19-20, 43, 50, 52-54, 58-61, 68-71 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

4. Claims 2-4, 12, 19, 20, 43, 52-54, 58-61 remain rejected under 35 USC 112, first paragraph and claims 68-69 and 71 are rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 9, Section 7, pages 4-7.

Applicant argues that (a) the specification discloses various nucleotide sequences encoding MEKK1 proteins and apoptotic fragments thereof and provides guidance for isolation, selection and identification of additional nucleic acid molecules and both the structure and function of these MEKK1 proteins and or fragments are described in detail as well as assays for MEKK1 activities, (b) enablement is not precluded by the necessity for some experimentation such as routine screening and any experimentation that may be required to make the claimed MEKK1 proteins or fragments constitutes routine and not undue experimentation. The arguments have been considered but have not been found persuasive (a')(b') the specification discloses SEQ ID Nos 3 and 4 which are mouse MEKK1 polynucleotide and polypeptide respectively while the claims encompass a broad

range of sequences which contain variants and portions of the single disclosed sequences. Variations in nucleic acid sequences are known in the art to be unpredictable for the reasons previously set forth. Given the data in the specification, the broadly written claims, the unpredictable nature of the art, the general nature of the teachings drawn to isolation, selection and identification, it appears that the artisan is left with random experimentation in order to practice the claimed invention. Random experimentation is undue. Applicant's arguments have not been found persuasive and the rejection is maintained.

New Grounds of Objection

5. Claim 58 is objected to because it is dependent upon claim 51 which was withdrawn from consideration in Paper No. 9, Section 2, page 2. Appropriate correction is required.

7. Claims 1-4, 19, 20 and 69 are objected to because they are dependent upon previously canceled claims 63-65. In the interests of compact prosecution, since it appears that the dependency of the claim was meant to be to newly added claims 68-70, it will be assumed for examination purposes that claims 1-5, 19, 20, 69 are meant to be dependent upon claims 68-70 as appropriate. Appropriate correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

6. Claims 1-4, 12, 19, 20, are rejected under 35 USC 112, first paragraph essentially for the reasons previously set forth in Paper No. 9, Section 7, pages 4-7 and further for the reasons set forth below because the specification, while being enabling for a polynucleotide comprising SEQ ID NO:3, a polynucleotide

completely complementary to the full length of SEQ ID NO:3 and a method of detecting MEKK1 nucleic acid molecule comprising contacting the sample with the complete, full length complement of SEQ ID NO:3, does not reasonably provide enablement for a complement of SEQ ID NO:3, a method for detecting the presence of MEKK1 nucleic acid comprising contacting the sample with a probe which selectively hybridizes to the nucleic acid molecule of claims 1 or 63-65 (renumbered under Rule 1.126 as claims 68-71). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to polynucleotides that (a) are a complement of SEQ ID NO:3, (b) a method for detecting the presence of a MEKK1 nucleic acid comprising contacting the sample with a nucleic acid probe that selectively hybridizes to the nucleic acid molecule of claim 1. This encompasses, any complement of SEQ ID NO:3, regardless of size or amount of complementarity and detection of any nucleic acid to which any size probe that selectively hybridizes to SEQ ID NO:3 or a complement thereof, regardless of its identity to a MEKK1 nucleic acid. The specification does not define "a complement". One cannot extrapolate the teaching of the specification to the scope of the claims because the specification does not provide teachings or working examples which would provide sufficient guidance to allow one of skill in the art to use the multitude of polynucleotide sequences encompassed by the scope of the claims. Clearly, it would be expected by one of ordinary skill in the art that a substantial number of the detected or complementary polynucleotides encompassed by the claims **would not** encode proteins that share either structural or functional properties with the protein encoded by SEQ ID NO:3

and it would not be expected that any of the polynucleotides without, complete be used in any of the methodsdescribed. Further, the specification does not provide either guidance on or exemplification of how to use the multitude of polynucleotides encompassed by the claims that do not encode proteins that share either structural or functional properties with SEQ ID NO:4. In view of the above, one of ordinary skill in the art would be forced into undue experimentation to practice the claimed invention.

7. If Applicant were able to overcome the rejections of claims 52-54 and 71 set forth previously and above, claims 52-54 and 71 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for a polynucleotide encoding a caspase-resistant MEKK1 protein, does not reasonably provide enablement for a polynucleotide encoding a protease-resistant MEKK1 protein as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are drawn to a polynucleotide encoding a protease-resistant MEKK1 protein wherein at least one codon encoding amino acids 871-873 is mutated. This includes resistance to all proteases. The specification teaches that MEKK1 active fragments are generated naturally by cleavage of MEKK1 by a caspase protease (p. 6, lines 1-20). Protease resistant forms of the protein can be generated by mutation of the caspase cleavage site corresponding to amino acids 871-874 of SEQ ID NO:4 such that the site cannot be cleaved by the caspase (p. 7, lines 5-8) . One cannot extrapolate the teaching of the specification to the scope of the claims because no cleavage site for a protease and no protease other than

caspase is taught in the specification. Examiner takes note of the fact that different proteases have different cleavage sites. Neither the specification nor the art of record teaches what other proteases could be used at this specifically claimed cleavage site or whether other cleavage sites useful for other proteases are found on the encoded protein which will function as claimed. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to make the claimed product with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention..

8. Claims 43 and all claims dependent upon claim 43 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a claimed in Claim 43 drawn to a fragment having 95% sequence identity to residues 875-1493 of SEQ ID NO:4 wherein % identity is determined over the entire length of residues 875-1493 of SEQ ID NO:4 has no clear support in the specification and the claims as originally filed. A review of the specification did not reveal support. The subject matter claimed in claims 43 and the claims dependent thereon broadens the scope of the invention as originally disclosed in the specification. Applicant is invited to point specifically to page and line where support for the newly added limitation can be found.

9. Claims 52 and all claims dependent upon claim 52 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a claimed in Claim 52 drawn to a sequence with at least 95% identity to SEQ ID NO:4 wherein % identity is determined over

the entire length of SEQ ID NO:1 .....after an amino acid equivalent to amino acid 874 of SEQ ID NO:4, has no clear support in the specification and the claims as originally filed. A review of the specification did not reveal support. The subject matter claimed in claims 52 and the claims dependent thereon broadens the scope of the invention as originally disclosed in the specification. Applicant is invited to point specifically to page and line where support for the newly added limitation can be found.

10. Claim 53 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation claimed in Claim 53 drawn to at least one codon is mutated to encode an alanine residue has no clear support in the specification and the claims as originally filed. A review of the specification did not reveal support. The subject matter claimed in claim 53 broadens the scope of the invention as originally disclosed in the specification. Applicant is invited to point specifically to page and line where support for the newly added limitation can be found.

11. Claim 54 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation claimed in Claim 54 drawn to each one codon is mutated to encode an alanine residue has no clear support in the specification and the claims as originally filed. A review of the specification did not reveal support. The subject matter claimed in claims 54 broadens the scope of the invention as originally disclosed in the specification. Applicant is invited to point specifically to page and line where support for the newly added limitation can be found.

12. Claims 52-54, 71 are rejected under 35 U.S.C. § 112, second paragraph, as

being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 52-54, 71 are indefinite because claim 52 is confusing in the recitation of "an amino acid equivalent". is Applicant claiming a conservative substitution that is mutated? Is Applicant claiming a substituent that is not an amino acid?. The claim is further confusing because the preamble of the claim is drawn to a "protease resistant MEKK1 protein while the body of the claim is drawn only to resistance to a caspase? It is unclear whether Applicant is claiming a caspase resistant protein or whether the protein is meant to be resistant to all proteases by mutation of at least one of the cited encoded amino acids?

Claim 71 is confusing because it is unclear whether claim 71 is drawn to a nucleic acid which encodes SEQ ID NO:4 or whether the claim is drawn to SEQ ID NO:4, wherein at least one codon encoding amino acids 871-874 are mutated.

Claim Rejections - 35 USC § 102

13. Claims 1-2, 4, 12, 19, 20, 43, 50, 58, 60 are rejected under 35 USC 102(b) as being anticipated by WO 94/241159, of record.

The claims are drawn to an isolated nucleic acid molecule comprising SEQ ID NO:3 or a complement thereof (claim 1) further comprising vector nucleic acid sequences (claim 2), a host cell containing said nucleic acid molecule (claim 4), a method of producing protein encoded by said nucleic acid molecule (claim 12) a method for detecting the presence of a MEKK1 nucleic acid comprising hybridization to the nucleic acid of claim 1 (claim 19), a kit comprising a compound which selectively hybridizes to the MEKK1 nucleic acid molecule of claim 1 (claim 20), an isolated nucleic acid molecules which encodes an active fragment of

MEKK1 that mediates apoptosis having 95% identity to residues 875-1493 of SEQ ID NO:4 (claim 43), a nucleotide sequence that due to the degeneracy of the genetic code encodes the same amino acid sequence as nucleotides 2637-4493 of SEQ ID NO:3 (claim 50), an expression vector comprising the nucleic acid of claim 43 (claim 58), a host cell containing the expression vector of claim 58 (claim 60).

It is noted that the specification does not define "complement thereof", therefore, it is assumed for examination purposes that the claimed complement thereof is not the complete full length complement but rather a nucleic acid molecule that is partially complementary to the nucleotide sequence of SEQ ID NO:3.

It is further noted that, although claims 50, 58 and 60 are drawn to a nucleotide sequence "consisting" as drawn the claimed specific fragment, the claim as written when drawn to a nucleotide sequence due to "degeneracy" of the genetic code, because of the structure of the claim, is not limited to a nucleotide sequence "consisting" and therefore it is assumed for examination purposes that the claimed limitation is met by a nucleotide sequence "comprising" said sequence.

WO 94/241159 teaches a nucleic acid molecule which is 99.9% identical to 61.8% of SEQ ID NO:3 (see sequence search us-09-403-075-3.rng, result 6). The complete complement of which would be instantly known to those involved in the art and which would be partially complementary to SEQ ID NO:3. The reference teaches the polynucleotide in a vector, in a host cell, methods of producing a protein, methods of detecting the polynucleotide and corresponding kits (see pages 50-59). Further, the nucleic acid sequence encodes an active fragment of with 100% identity to residues 875-1493 (see sequence search us-09-403-075-4.p2n.rng, p. 15-17) and which therefore inherently has the claimed functional property which

due to the degeneracy of the genetic code encodes the same amino acid sequence as nucleotides 2637-4493 of SEQ ID NO:3 as well as expression vectors and host cells containing the expression vector as set forth above (see sequence search us-09-403-075-3.rng, result 6 and us-09-403-075-4.p2n.rng, p. 15-17). All of the limitations of the claims are met.

14. Claims 1, 20 are rejected under 35 USC 102(b) as being anticipated by Boehringer Mannheim Biochemicals, 1994 Catalog, p. 93).

The claims are drawn to a nucleic acid molecule which is a complement of SEQ ID NO:3 (claim 1), a kit comprising a compound which selectively hybridizes to the MEKK1 nucleic acid molecule of claim 1 and instructions for use (claim 20).

The Boehringer Mannheim teaches a kit and instructions for use thereof comprising random primers that encompass all possible 6-nucleotide sequences (see page 93, Catalog No. 1034 731/1006 924), and therefore a subset of the random primers would include the complement of the claimed polynucleotide. Since the specificity of selective hybridization depends upon hybridization, since a subset of the primers would hybridize completely, these primers are clearly selective for those sequences. All of the limitations of the claims are met.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject

matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

16. Claims 1, 3 are rejected under 35 USC 102(b) as being obvious over WO 94/241159, of record and further in view of US Patent No. 5,968,781.

The claims are drawn to an isolated nucleic acid molecule comprising SEQ ID NO:3 or a complement thereof (claim 1), further comprising nucleic acid sequences encoding a heterologous polypeptide (claim 3).

WO94/241159 teaches as set forth above but does not teach a nucleic acid further comprising sequences encoding a heterologous polypeptide.

US Patent No. 5,968,781 teaches a recombinant molecule comprising a polynucleotide encoding a protein which further comprises nucleotide sequences encoding a histidine tag inserted into the 5' terminus or 3' terminus of the gene and further teaches that the tag prevents degradation of the recombinant protein and facilitates purification of the protein by histidine tag affinity column as a metal chelating affinity column (col 3, lines 16-25).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of WO 94/241159 above and US Patent No. 5,968,781 to produce a recombinant polynucleotide encoding a protein with a histidine tag because histidine tags are conventionally used to facilitate purification of the recombinant protein. One of ordinary skill in the art at

the time the invention was made would have been motivated to combine the methods of WO 94/241159 above and US Patent No. 5,968,781 in order to easily recover the expressed polypeptide and in order to stabilize the protein in solution.

17. Claim 70 appears to be free of the art and allowable.

18. All other objections and rejections recited in Paper No. 9 are withdrawn.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
March 5, 2003